Rejection Under 35 U.S.C. §112, first paragraph: written description.

Claims 1-14 and 16-22 stand rejected under 35 U.S.C. §112, first paragraph, for failing to describe in sufficient detail to clearly convey to those skilled in art that Applicants had possession of the claimed subject matter. Applicants respectfully traverse.

In an initial issue, the Examiner suggests that "modulators of HO-1" are not clearly defined in the specification such that given its "plain meaning" the term is not restricted to HO-1 variants and may encompass generic agents and compounds, varying in sequence or chemical structures. Thus, the conclusion is drawn that a skilled artisan "cannot envision the sequences or chemical structures of the genus of modulators for HO-1." Applicants respectfully disagree.

In determining compliance with the written description requirement, the examination guidelines provide that each claim must be examined as a whole and be "given its broadest reasonable interpretation in light of and consistent with the written description." See M.P.E.P. §2163 ("claim construction is an essential part of the examination process"). In construing claims, the Federal Circuit has held that

> [a]lthough words in a claim are generally given their ordinary and customary meaning, a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition is clearly stated in the patent specification . . . .

See Vitronics Corp. v. Conceptronic, Inc., 39 USPQ2d 1573, 1576 (Fed. Cir. 1996). Consequently, it is encumbent upon the Examiner to review the specification to "determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning." See Id. at 1577. When the applicant provides a definition in the specification for the claim terms, the definition selected by the applicant controls, especially in cases where "there may not be an extant term of singular meaning for the structure or the concept being

claimed," as long as the term is defined with "reasonable clarity, deliberateness, and precision." See Renishaw plc v. Maposs Societa' per Azioni, 48 USPQ2d 1117, 1121 (Fed. Cir. 1998). Thus, if the common meaning is contrary to the intended meaning in the patent disclosure, or where there are several common meanings for a given claim term, the patent acts as a guide toward proper construction of the claim term. See id. at 1122; see also Vitronics Corp., 39 USPQ2d at 1577 ("The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication. . . . It is the best guide to the meaning of a disputed term").

In view of the foregoing, the phrase "modulators of HO-1" must be read in context of the entire claim. In this regard, claim 1 recites "nucleic acid that modulates heme oxygenase-I activity" rather than simply "modulators of HO-I." Since claims must be read in view of the specification, Applicants direct the Examiner to page 5, lines 10-17 of the specification, which states

> For the most part, nucleic acid molecules that function to modulate HO-1 activity in cells will be nucleic acid molecules that encode a polypeptide that exhibits at least one biological activity that is normally associated with the human HO-1 polypeptide encoded by nucleotides 81-944 of the nucleic acid shown in Figure 3 (SEQ ID NO: 1) or will be antisense oligonucleotides whose sequences are derived from and/or based upon nucleotides 81-944 of the human heme oxygenase-I nucleotide sequence shown in Figure 3 (SEQ ID NO: 1) or non-coding sequences of a heme oxygenase-encoding nucleic acid molecule.

The specification on page 5, lines 18-25 and page 9, lines 10-14 further delineates "heme oxygenase-I":

> By "heme oxygense-I", "HO-1" and grammatical equivalents thereof is meant the polypeptide encoded by nucleotides 81-944 of the nucleotide sequence shown in Figure 3 (SEQ ID NO: 1) and homologs thereof which exhibit at least one biological activity that is normally associated with the human heme oxygenase enzyme. Preferably, the heme oxygenase-I activity exhibited by the polypeptides is the ability to catalyze the first step in the oxidative degradation of heme to

> bilirubin. . . . Heme oxygenase-I having less than 100% sequence identity with the polypeptide encoded by nucleotide 81-944 of the nucleotide sequence shown in Figure 3 (SEQ ID: 1) *will generally be produced from native heme oxygenase-I nucleotide sequences from species other than human and variants of native heme oxygenase-I nucleotide sequences from human or non-human sources.*

(emphasis added). The specification describes with particularity homologous peptide molecules with heme oxygenase-I activity (page 6, lines 16-21):

> Also encompassed by "heme oxygenase-I", "HO-I", etc. are homolog polypeptides having at least about 80% sequence identity, usually at least about 85% sequence identity, preferably at least about 90% sequence identity, more preferably at least about 95% sequence identity and most preferably at least about 98% sequence identity with the polypeptide encoded by nucleotides 81-944 of the nucleotide sequence shown in Figure 3 (SEQ ID NO: 1) and which exhibit at least one biological activity that is normally associated with human heme oxygenase-I enzyme.

In similar language, the specification delineates nucleic acid molecules encoding heme oxygenase-I (page 6, lines 22-29 and page 7, lines 1-2):

> By "nucleic acids molecules that encode [H]O-I", "nucleic acid molecules encoding a polypeptide having heme oxygenase-I activity" and grammatical equivalents thereof is meant the nucleotide sequence of human heme oxygenase-I as shown nucleotides 81-944 of Figure 3 (SEQ ID NO: 1) as well as nucleotide sequences having at least about 80% sequence identity, usually at least about 85% sequence identity, preferably at least about 90% sequence identity, more preferably at least about 95% sequence identity and most preferably at least about 98% sequence identity with nucleotides 81-944 of the nucleotide sequence shown in Figure 3 (SEQ ID NO: 1) and which encode a polypeptide that exhibits at least one biological activity that is normally associated with the human heme oxygenase-I enzyme.

In keeping with the scope of "nucleic acid modulators of heme oxygenase-I" as described above, the specification goes on to describe some variants of heme oxygenase-I with particularity (page 9, lines 19-28):

> Polypeptides having heme oxygenase-I activity may be shorter or longer than the polypeptide encoded by nucleotides 81-944 of the nucleotide sequence shown in Figure 3 (SEQ ID NO: 1). Thus, in a preferred embodiment, included within the

> definition of heme oxygenase-I polypeptide are portions or fragments of the polypeptide encoded by nucleotide 81-944 of the nucleotide sequence shown in Figure 3 (SEQ ID NO: 1). In one embodiment herein, fragments of the polypeptide encoded by nucleotides 81-944 of the nucleotide sequence shown in Figure 3 (SEQ ID NO: 1) are considered heme oxygenase-I polypeptides if a) they have at least the indicated sequence identity; and b) preferably have a biological activity of naturally occurring heme oxygenase-I, as described above.

Other variants of heme oxygenase-I are also given (page 11, lines 18-30):

> In one embodiment, the present invention provides nucleic acids encoding heme oxygenase-I variants. These variants fall within one or more of three classes: substitutional, insertional or deletional variants. . . . Amino acid sequence variants are characterized by the predetermined nature of the variation, a feature that sets them apart from naturally occurring allelic or interspecies variation of heme oxygenase-I amino acid sequence. The variants typically exhibit the same qualitative biological activity as the naturally occurring analogue, although variants can also be selected which have modified characteristics . . . .

As evidenced from the disclosure, Applicants have clearly circumscribed the nature of nucleic acid modulators of heme oxygenase-I activity in cells. The phrase is neither arbitrary nor ambiguous since the specification uses the terms consistently and provides proper guidance on construing the proper scope of the phrase. Nucleotide sequence of an exemplified "nucleic acid modulator of heme oxygenase-I" is given in Figure 3, including the noncoding region and the segment encoding the human heme oxygenase-I polypeptide. Persons skilled in the art can readily obtain the complementary antisense nucleic acid or translate the given nucleotide sequence segment to obtain the amino acid sequence for the described heme oxygenase.

On the whole, the specification does not refer to any generic nucleic acid but specifically and consistently discloses the function and structure of the claimed nucleic acid modulators of heme oxygenase-I activity. As stated by the Federal Circuit, "[t]he construction that stays true to the claim language and most naturally aligns with the patent's

description of the invention will be, in the end, the correct construction." See Renishaw plc, 48 USPQ2d at 1122. Accordingly, Applicants respectfully submit that the claims when read in the context of the specification describe with particularity and distinctly define the scope of nucleic acid modulators of heme oxygenase-I activity in cells.

Although the specification provides a clear description of the structure and function of the nucleic acids modulators of HO-1, the Examiner suggests that recitation of a single species of heme oxygenase-I is insufficient to satisfy the written description requirement. The Examiner cites the Interim Guidelines, which state "the claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art." Applicants respectfully traverse.

The M.P.E.P. §2163 (II)(3)(a)(ii) provides that for claims drawn to a genus, the written description requirement may be "satisfied through sufficient description of representative number of species by actual reduction to practice, . . . disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of identifying characteristics, sufficient to show applicant was in possession of the claimed genus." The Federal Circuit, however, has also held that description of a representative number of species "does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." See Regents of University of California v. Eli Lilly, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); see also M.P.E.P. § 2163 (II)(3)(a)(ii). With this view, the Federal Circuit in Eli Lilly further stated that "description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence falling

within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus" 43 USPQ2d at 1406.

Determining what constitutes a representative number of species sufficient to support a genus depends on whether one skilled in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. See M.P.E.P. §2163 (II)(3)(a)(ii). Information which is well known in the art need not be described in detail in the specification to satisfy the written description requirement. See M.P.E.P. §2163(II)(A)(2). Consequently, an applicant need not disclose every detail of the invention if a person skilled in the art would understand from the description that an applicant was in possession of the claimed subject matter at the time of filing of the application.

In the instant application, heme oxygenases comprise a well known group of enzymes. The specification discloses a review article that explains the characteristics of heme oxygenases, including catalytic activities associated with this class of enzymes and their structure (Exhibit A, Abraham, N.G. *et al.* (1988) Int. J. Biochem. 20: 543-558). Other prior art cited in the specification describes the role of heme oxygenases in physiological responses to stress (Exhibits B and C, Raju, V.S and Maines, M.D. (1994) Biochim Biophys Acta 1217: 273-80 and Willis, D. *et al.* (1996) Nat. Med. 2: 87-90, respectively).

Moreover, the nucleic acids and their encoded proteins comprising the family of "heme oxygenases" were well known at the time of filing of the instant application. A search of the NCBI Genbank database for enzymes comprising heme oxygenases reveals nucleic acid and amino acid sequences for rat heme oxygenase-I (Accession No. AAA41346, Mueller, R.M. *et al.* (1987) J. Biol. Chem. 262: 6795-6802); mouse heme oxygenase-I

(Accession No. P14901, Kageyama, H. *et al.* (1988) Cancer Res. 48: 4795-4798); human heme oxygenase-I (Accession No. CAA30045, Yoshida, T. *et al.* (1988) Eur. J. Biochem. 171: 457-461); porcine heme oxygenase-I (Accession No. CAA43092, Suzuki, T. *et al.* (1992) Biochem. Int. 28: 887-893); chick heme oxygenase-I (S15123, Evans, C.O. *et al.* (1991) Biochem. J. 273: 659-666); and *Arabidopsis thaliana* heme oxygenase-I (Accession No. AAD22107, Davis, S.J. *et al.* (1999) Proc. Natl. Acad. Sci. USA 96: 6451-6546).[1]

Furthermore, nucleotide and protein sequences for heme oxygenase-2, the non-inducible form which is homologous to heme oxygenase-I and displays the same enzymatic activity, were also known for human heme oxygenase-2 (Accession No. AAB22110, McCoubrey, W.K. *et al.* (1992) Arch. Biochem. Biophys. 295: 13-20); mouse heme oxygenase-2 (Accession No. AAC82364, Gibbs, L. *et al.* (1998) Gene 221: 171-177 and Matsumoto, M. (1996) J. Biochem (Tokyo) 120: 1079-81); rabbit brain heme oxygenase-2 (Accession No. AAB20093, Rotenberg, M.O. *et al.* (1991) Arch. Biochem. Biophys. 290: 336-344); and rat heme oxygenase-2 (Accession No. AAA19130, McCoubrey, W.K. *et al.* (1994) Gene 139: 155-61). More distantly related heme oxygenases were identified for, among others, heme oxygenase-3 (Accession No. AAC14142, McCoubrey,W.K. *et al.* (1997) Eur. J. Biochem. 247: 725-732), *Synechococcus sp.* (Accession No. AAD02480), *Rhodella violacea* (Accession No. AAB66516, Richaud, C. (1997) Proc. Natl. Acad. Sci. USA 94: 11736-41), and *Corynebacterium diptheriae* (Accession No. AAC44832, Schmitt, M.P. (1997) J. Bacteriol. 179: 838-845).

It is clear from the characterizations of heme oxygenase and the number of sequence

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[1] Although Applicants have provided accession numbers for amino acids sequences of heme oxygenases, the corresponding nucleotide sequences are readily accessed using the hypertext links provided in the NCBI sequence database.

entries in the NCBI database at the time of filing that this class of enzymes were well known in the art in relation to their catalytic activity, nucleotide sequence, and amino acid sequence. As further support, Applicants provide herein Exhibit D, Evans, C-O. *et al.*, "Cloning, sequencing and expression of cDNA for chick liver haem oxygenase: Comparison of avian and mammalian cDNAs and deduced proteins," Biochem. J. 273: 659-666 (1991), an early article examining nucleic acids encoding heme-oxygenases, in particular heme oxygenase-I. The study describes the cloning and sequencing of chick liver heme oxygenase-I. Overall degree of amino acid similarity is found to be 62% between chick and rat, 62% between chicken and human, and 79% between human and rat. The degree of similarity in the nucleotide sequence is 66% between chick and rat, 66% between chick and human, and 81% between rat and human. This high level of similarity of rat and human nucleotide sequences is exemplified in Exhibit E, Yoshida, T. *et al.* "Human heme oxygenase cDNA and induction of its RNA by hemin," Eur. J. Biochem. 171: 457-461 (1988), in which nucleic acids coding for human heme oxygenase in macrophages were identified using a nucleic acid probe derived from rat heme oxygenase cDNAs. Expression in *E. coli.* of nucleic acids encoding heme oxygenases and the presence of heme oxygenase activity, i.e., conversion of heme to bilirubin, in these expressing cells clearly show that the nucleic acids in fact encode heme oxygenase enzyme (see Exhibit D, page 665 and Exhibit F, Ishikawa, K. *et al.* "Expression of rat heme oxygenase in *Escherichia coli* as a catalytically active, full length form that binds to bacterial membranes," Eur. J. Biochem. 202: 161-165 (1991)).

Based on the descriptions of nucleic acid modulators of heme oxygenase-I activity given in the specification and the wealth of available knowledge of heme oxygenase enzymes, a person skilled in the art could readily envisage the nucleic acid modulators encompassed by the present claims. Applicants have clearly elaborated a catalytic activity

associated with heme oxygenase-I, provided the nucleotide sequence of an exemplary heme oxygenase (i.e., human heme oxygenase-I) and by implication its amino acid sequence, and disclosed a working example using a rat heme oxygenase-I (specification, Example 3), which is homologous to the disclosed human heme oxygenase-I sequence. The family of heme oxygenases are known by their common enzymatic activity, conserved amino acid sequences in a substantial portion of the genus, and for many species by high degree of similarities in nucleic acid sequences. Since many heme oxygenase nucleic acid sequences were known, a person skilled in the art had knowledge of a sufficiently representative number of heme-oxgenase nucleic acid and polypeptide sequences such that Applicants clearly conveyed to a skilled artisan that Applicants were in possession of the claimed subject matter at the time of filing. Accordingly, Applicants submit that the disclosure satisfies the written description requirement under 35 U.S.C. §112, first paragraph for claims 1-22.

In further regards to claims 13-22, the Examiner finds the phrase "nucleic acids having HO-1 activity" or "nucleic acids having at least 80% sequence identity to nucleotides 81-944 of SEQ ID NO: 1 and having biological activity of human HO-1" is not sufficiently described in the specification to satisfy the written description standard. In particular, the Examiner contends that one skilled in the art would not know what changes to make in the nucleotide sequence of heme oxygenases to arrive at a nucleic acid having at least about 80% homology to SEQ ID NO: 1 and which encodes a variant polypeptide having heme oxygenase-I activity since the "significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Applicants respectfully traverse.

As discussed above, Applicants have shown that the heme oxygenase class of enzymes were well known in the art as to their nucleotide and amino acid sequences. Since

methods for aligning and comparing the nucleic acid and amino acid sequences were well known in the art, and are provided in detail in the specification (specification, pages 7-9), a person skilled in the art could readily identify conserved amino residues important for protein structure and enzymatic activity.

As shown in Exhibit D, a high degree of amino acid sequence conservation is found between heme oxygenases isolated from different species. Regions of conservation are found for even distantly related heme oxygenase polypeptides with much less than 80% amino acid sequence homology to human heme oxygenase-1 (Exhibit G, Schmitt, M. "Utilization of Host Iron Sources by *Corynebacterium diphtheriae*: Identification of a Gene Whose Product is Homologous to Eukaryotic Heme Oxygenases and Is Required for Acquisition of Iron from Heme and Hemoglobin," J. Bacteriol. 179: 838-845 (1997)). Sequence comparison of the isolated *Corynebacterium* heme oxygenase with human heme oxygenase sequence identifies, among others, a conserved 24 amino acid region (residues 126-149) important for catalytic activity. The conservation of this heme interacting region was found in early studies of heme oxygenases as shown in Exhibit H, Rotenberg, M.O. and Maines, M.D., "Characterization of a cDNA encoding rabbit brain heme oxygenase-2 and identification of a conserved domain among mammalian heme oxygenase isozymes: possible heme binding site?", Arch. Biochem. Biophys. 290: 336-44 (1991). This article compared amino acid sequences of heme oxygenase-I from rat, mouse, and human, and heme oxygenase-2 of rat to the amino acid sequence of the isolated rabbit heme oxygenase-2 and identified a twenty four amino acid region in both heme oxygenase-I and heme oxygenase-2 exhibiting 96% similarity in sequence and 100% similarity in predicted secondary structure. The solving of the X-ray crystallographic structure, as described below, confirms that this conserved region is involved in heme binding and is critical to enzyme activity. The carboxy terminal region, which is not

conserved, is found not to be critical to enzyme activity since variants lacking twenty three amino acids of the carboxy terminus display heme oxygenase catalytic activity indistinguishable from native enzyme (Exhibit I, Wilks, A. "Rat Liver Heme Oxygenase: High level expression of a truncated soluble form and nature of the meso-hydroxylating species," J. Biol. Chem. 268: 22357-62 (1993)).

In addition, the relationship between the amino acid sequence and three dimensional structure of heme oxygenases were also well known in the art. The Examiner is directed to Exhibit J, Schuller, D.J. *et al.* "Crystal structure of heme oxygenase-1," Nat. Structural Biol. 6: 860-867 (1999) and Exhibit K, Omata, Y. *et al.*, "Crystallization and preliminary X-ray diffraction studies on the water soluable form of rat heme oxygenase-1 in complex with heme," Acta Crystallogr. D54: 1017-1019 (1998) , both of which were published before the filing date of the instant application. Exhibit J describes the X-ray crystallographic structure of human heme oxygenase-I while Exhibit K describes crystallographic structure of the rat heme oxygenase-I. In both cases, the structures were deduced for enzymes bound to substrate heme. Schuller, *et al.* discusses the role of various conserved residues in heme binding, ligand discrimination, and catalytic activity and correlates the deduced three dimensional structure with the results of various mutational studies of heme oxygenases. Schuller, *et al.* also states

> [a]ll of the known heme oxygenase enzymes are homologous and from sequence alignment are expected to share the same fold and mechanism. The sequences align well throughout the length of the soluble, 215 residue *C. diptheria* enzyme. Many other forms, including human HO-1 and HO-2, contain C-terminal extensions with membrane anchors, and the sequences diverge after approximately residue 220 of human HO-1. The sequence identity between human HO-1 and HO-2 is 45% for the full length and 56% for the conserved core of the enzyme. Among the known HO sequences, the *Arabidopsis* HO is the farthest from human HO-1, with 21% identity, while the *C diptheria* enzyme is the second farthest, but still shares 36% identity with it.

(page 860, right column, lines 8-20).

Given the knowledge of heme oxygenase structures and the established regions of homology between heme oxygenase proteins, a person skilled in the art would be able to identify particular amino acid residues critical to enzyme activity when making substitutional, insertional, or deletional variants. Conservative substitutions may be made for those residues critical to activity while more profound changes may be made for less conserved residues. The specification provides direction and guidance for making these substitutions (specification, page 12-13). Importantly, the art of record show that heme oxygenase variants were already made and known in the art prior to filing of the instant application.

Applicants reiterate that even if some constructed variants may be inoperable, "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render the claim non-enabled" if a skilled artisan "could determine which embodiments that were conceived, but not yet made would be inoperative with expenditure of no more effort than is normally required in the art." See Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 224 USPQ 409, 414 (Fed. Cir. 1984). In the instant case, given the knowledge of heme oxygenases, a skilled artisan making the variants can readily identify those having the requisite activity from those that do not without undue experimentation.

In summary, Applicants submit that the claims, when read in view of the specification, sufficiently circumscribe the scope of "nucleic acids that modulate heme oxygenase-I activity in cells," thus providing a sufficient written description of the claimed subject matter. In particular, the specification discloses common features possessed by heme oxygenase-I or homologs (e.g., the ability to catalyze the first step in the oxidative degradation of heme to bilirubin), discloses a specific nucleotide sequence for an exemplary

human heme oxygenase-I from which a person skilled in the art could readily obtain the amino acid sequence, specifically describes heme-oxygenase-1 variants and homologs within the limitations of the science and the language, and provides a working example using rat heme oxygenase-I, a homolog of the disclosed human heme oxygense-I. Based on these descriptions, those skilled in the art would have been aware of the nucleotide and corresponding amino acid sequences of other heme oxygenases without undue experimentation.

Moreover, the wealth of knowledge about conserved amino acid residues in the heme oxygenase proteins, the availability of structural information regarding heme oxygenase-I, and the high skill in the art for identifying and making variants encoding a polypeptide with functional heme oxygenase activity would allow a person skilled in the art to readily identify other members of the genus being described for the claimed subject matter. Thus, Applicants have provided sufficient written description to convey to the skilled artisan that Applicants had possession of the claimed subject matter at the time of filing.

Based on all of the foregoing, Applicants have provided the necessary specificity required to comply with the written description standard. A person skilled in the art would clearly understand from the disclosure the description of nucleic acid modulators of heme oxygenase-1 activity or nucleic acids encoding a polypeptide having heme oxygenase-I activity. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-22 under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §112, first paragraph: Enablement

Claims 1-14 and 16-22 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner contends that the claimed method for extending the survival of

an organ transplant is enabled for a nucleic acid (SEQ ID NO: 1) encoding human heme oxygenase-I but is not enabled for nucleic acids having about 80% nucleic acid sequence identity to SEQ ID NO: 1 or a nucleic acid that modulates HO-1 activity. The Examiners position appears to be that a perceived failure to describe the broad class of nucleic acids that modulate HO-1 activity or describe sequences sharing the indicated sequence identity does not enable practice of the claimed methods without undue experimentation. Applicants respectfully traverse.

As the Examiner is well aware, the M.P.E.P §2164.04 provides that

> [a] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In addition, the scope of enablement need only bear a reasonable relationship to the scope of the claims. See In re Fischer, 166 USPQ 18, 24 (CCPA 1970). For a claimed genus,

> representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in a manner without undue experimentation. Proof of enablement will be required for other members of the genus only where adequate reasons are advanced to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

In the instant case, Applicants respectfully submit that an objective rationale has not been provided as to why heme oxygenase-I homologs or variants encoding a polypeptide having heme oxygenase activity, or the nucleic acid modulators as delineated in the specification, would not function in prolonging the survival of organ transplants by modulating cellular levels of heme oxygenase-I. In the disclosure, Applicants have provided a specific working example where expression of rat heme oxygenase-I, which is homologous

to the disclosed human heme oxygenase-I, prolonged survival of organ transplants in rats. The protective effects of increasing heme oxygenase-I activity in organ transplants by infection with an adenoviral vector expressing heme oxygenase-I mimics the protective effects induced by treatment with metalloprotoporphyrins which increase heme oxygenase-I activity. Thus, Applicants have directly shown that a homolog of the human sequence functions as claimed in extending the survival of organ transplants.

Moreover, by providing a specific description of the scope of the claimed subject matter, Applicants have conveyed to those skilled in the art the class of nucleic acids modulating heme oxygenase-I and nucleic acids encoding heme oxygenases that were well known in the art. It is well settled that an applicant need not disclose, and preferably omits what is well known in the art since he is speaking to those skilled in the art:

> [T]he applicant may begin at the point where his invention begins, and describe what he has made that is new and what it replaces of the old. That which is common and well known is as if it were written out in the patent and delineated in the drawings

See PPG Indus. v. Guardian Indus. Corp., 37 USPQ2d 1618 (Fed. Cir. 1996); see also In re Buchner, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); see also DeGeorge v. Bernier, 226 USPQ 758, 762 (Fed. Cir. 1985).

Applicants further submit that the methods for making substitutional, insertional, and deletional variant polypeptides having heme oxygenase activity are well known in the art. The skill for making amino acid sequence variants is high and the art typically engages in such experimentation, which is evidenced by the variants described in the exhibits. Thus, making the variants were well within the ordinary skill in the art. As emphasized by the Federal Circuit

> [t]he determination of what constitutes undue experimentation in a given case

> requires the application of a standard of reasonableness . . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction of which the expectation should proceed.

See In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In addition, the Federal Circuit has stated that "structural relationships often provide the requisite motivation to modify known compounds to obtain new compounds." See In re Mayne, 41 USPAQ2d 1451, 454 (Fed. Cir. 1997). In Mayne, the court held that because of the chemical and structural similarities between Leucine (Leu) and Isoleucine (Iso), replacement of Iso with Leu in a cleavage sequence recognized by the protease enterokinase resulted in an obvious functional equivalent to other enterokinase recognition sequences disclosed in the prior art. The court described the relationship between Leu and Ile:

> an identical chemical formula with differences only in the chemical bonding of atoms. The side chains, also known as R groups, of Leu and Ile have the same number of hydrogen and carbon atoms. Both are non-polar, hydrophobic amino acids. The structure of Leu and Ile alone suggest their functional equivalency.

Since the prior art showed enterokinase recognition sequences had either Ile or Leu at the third position of the peptide denoted by X, the court held that the prior art also suggested substitutions of Leu for Ile at the third position of other recognition sequences having different peptide X sequence. Thus, the Federal Circuit recognizes that a person skilled in the art can obtain variants of a protein sequence given the knowledge of the structure of the family of similar peptide sequences.

Similarly, Applicants submit that the knowledge of numerous heme oxygenases and the their structure, and the knowledge of conserved amino acid residues between known heme oxygenases allows a person skilled in the art to make variants that would be reasonably expected to function in the expected manner without undue experimentation.

In further support that practice of the claimed methods are enabled without undue experimentation, Applicants provide articles published subsequent to filing of the present application showing operability of nucleic acid modulators or nucleic acids encoding a heme oxygenase. See M.P.E.P §2164.05(A); see also In re Wilson, 135 USPQ 442, 444 (CCPA 1962); see also Ex parte Obukowicz, 27 USPQ2d 1063 (BPAI 1993); see also Gould v. Quigg, 3 USPQ2d 1302 (Fed. Cir. 1987):

> it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the later dated publication was not offered as evidence of this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative.

Applicants direct the Examiner to Exhibit L, Hegazy, K.A. "Functional human heme oxygenase has a neuroprotective effect on adult rat ganglionic cells after pressure induced ischemia," NeuroReport 11: 1185-1189 (2000), which demonstrates that infection of rat retina with an adenoviral vector expressing a functional human heme oxygenase-I significantly increased survival of rat retinal ganglionic cells in retinas subjected to ischemia and reperfusion. Applicants note that rat and human heme oxygenase have about 79% nucleic acid sequence identity and about 81% amino acid sequence similarity (see Exhibit D, Evans, *et al.*, supra). Expressing human heme oxygenase-I in rats through an adenoviral expression vector also protects rat hearts from ischemia induced myocardial injury (Exhibit M, Melo, L.G. *et al.*, "Gene Therapy Strategy for Long-Term Myocardial Protection Using Adeno-Associated Virus Mediated Delivery of Heme Oxygenase Gene," Circulation 105: 602-607 (2002), while expression of the human heme oxygenase-I in mice functions to protect Apolipoprotein-E deficient mice from developing atherosclerosis (Exhibit N, Juan, S-H., "Adenovirus-Mediated Heme Oxygenase-1 Gene Transfer Inhibit the Development of Atherosclerosis in Apolipoprotein E Deficient Mice," Circulation 104: 1519-1525 (2001).

Conversely, expressing rat heme oxygenase-I in human cells results in modulation of heme oxygenase activity in these cells. Applicants direct the Examiner to Exhibit O, Lee. P.J. "Overexpression of heme oxygenase-1 in human pulmonary epithelial cells results in cell growth arrest and increased resistance to hypoxia," Proc. Natl. Acad. Sci. USA 93: 10393-98 (1996). which shows that expression of rat heme oxygenase-I in human pulmonary epithelial cells results in increased survival when the cells are subjected to hypoxia. Similarly, Exhibit P, Hori, R. "Gene Transfection of H25A Mutant Heme Oxygenase-1 Protects Cells against Hyperoxide-induced Cytotoxicity," J. Biol. Chem. 277: 10712-10718 (2002) shows that expression of rat heme oxygenase-I in human lymphoma cell lines alters the susceptibility of these cells to peroxides as a result of changes in cellular heme oxygenase-I activity. Moreover, Exhibit 18 provided in the response filed October 15, 2001 (Paper #9) describes infection of human HeLa cells with adenoviral vector expressing rat heme oxygenase-I and the conferring of protection from cell death triggered by Fas and Fas ligand. These studies show that a nucleotide sequence with at least about 80% sequence identity to human heme oxygenase and which encodes a polypeptide having heme oxygenase activity produces physiological effects attributable to increases in cellular heme oxygenase activity.

In view of the above, Applicants submit that the disclosure for practicing the claimed method and the working examples bears a reasonable correlation to the entire scope of the claim. The claimed genus could be used in the manner described without undue experimentation. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-22 under 35 U.S.C. §112, first paragraph.

CONCLUSION

Applicants submit that all pending claims of the above referenced application are in

compliance with all the requirements of patentability and are in condition for allowance. Accordingly, early notification of such allowance is earnestly solicited.

If after review, the Examiner feels there are further unresolved issues or determined that prosecution of the above reference application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

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Date 6/26/02

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